

## **REMARKS**

### **Claim Amendments**

Applicants have amended claim 27 to recite a method for reducing memory dysfunction associated with damaged hippocampal tissue in a mammal “and caused by permanent or transient global ischemia.” Support for this amendment may be found, *inter alia*, in Example 8 (page 46, lines 3-19) and Example 9 (page 46, line 20 to page 47, line 14) of the specification as originally filed. Applicants have amended claims 34 and 35 to replace specific residues of SEQ ID NO:2 with “a mature form of human OP-1.” Support for this amendment may be found, *inter alia*, on page 8, lines 6-9 of the specification as originally filed. Applicants have amended claim 46 to delete reference to ethanol or lead. Lastly, Applicants have redrafted claims 46 and 48 as independent claims.

Applicants have added new claims 51-53. Support for these new claims may be found, *inter alia*, on page 4, lines 21-24.

Applicants have canceled claims 39-42, 45, 47, 49 and 50, merely to expedite allowance, without prejudice to Applicants’ right to pursue the subject matter of these claims in a continuation application.

These amendments do not introduce any new matter. Entry of these amendments is requested such that claims 27-32, 34-38, 43, 44, 46, 48 and 51-53 will be pending.

### **Priority**

The Office Action maintains that the specification as filed does not provide support for claims 34 and 35, which recite portions 293-431 and 30-431 of SEQ ID NO:2, respectively. The Office Action alleges that the parent application does not specifically recite these ranges, and concludes that these two claims are only entitled to the December 12, 2003 filing date of the subject application, rather than to the January 23, 1998 filing date of the parent application. The Examiner acknowledges proper support for ranges 330-431, 30-292 and 48-292.

Applicants traverse this ground of rejection. However, in order to expedite allowance of the claims, Applicants have amended claims 34 and 35 to replace the ranges with “the mature form of human OP-1.” The specification recites on page 8, lines 6-9 that “[u]seful forms of the protein

include, for example, *the mature form* of the morphogen provided alone or provided in association with its precursor "pro" domain, which is known to enhance the solubility of the protein."

(Emphasis added.)

Based on this amendment, Applicants request reconsideration and withdrawal of this ground of rejection.

### **Information Disclosure Statement**

The Examiner requests that legible copies be provided of all nonpatent references and non-U.S. patent references cited in the IDS filed February 12, 2004. Under 37 CFR § 1.98(d), however, Applicants are relieved of their burden to provide copies of nonpatent references and of non-U.S. patent references if the references were cited by the Examiner or provided by Applicants in an IDS in an application from which the subject application claims priority under 35 U.S.C. § 120. All of the requested references were either previously submitted by Applicants or cited by the Examiner in the parent application (Ser. No. 09/012846) from which the instant application claims priority under 35 U.S.C. § 120. Applicants point the Examiner to the Information Disclosure Statement filed in the parent application on January 23, 1998, and to the references cited by the Examiner on September 2, 1999; August 21, 2001; June 18, 2002; October 21, 2003; and January 26, 2004. Accordingly, Applicants are relieved of the burden to provide the references. Applicants respectfully request that the Office retrieve copies of the requested references from the parent application.

### **Oath and Declaration**

The Office Action requests that a new Oath and Declaration be submitted on the grounds that the specification allegedly contains new matter in claims 34 and 35 not present in the parent application. In response, Applicants note that the alleged new matter in claims 34 and 35 has been removed, as indicated in a previous section of this amendment. Applicants respectfully request reconsideration and withdrawal of this ground of rejection.

### **Specification**

The Office Action objects to the preliminary amendment filed with the application as allegedly adding new matter contrary to 35 U.S.C. § 132(a). Specifically, the Office Action objects to the recitation of segments 293-431 and 30-431 of SEQ ID NO:2 in claims 34-35. In response, Applicants note that the alleged new matter in claims 34 and 35 has been removed, as indicated in a previous section of this amendment. Accordingly, the subject matter of the claims is fully supported by the originally-filed specification. Applicants respectfully request reconsideration and withdrawal of this ground of rejection.

### **Anticipation rejection under 35 U.S.C. § 102(b) (Withdrawn)**

Applicants acknowledge that the Examiner has deemed all pending claims to be novel over Withers et al.

### **Enablement rejection under 35 U.S.C. § 112**

The Office Action maintains the rejection of claims 27-38, and further rejects claims 39-50, under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the enablement requirement.

MPEP 2164.04 states that "[i]n order to make a rejection, the Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." Under MPEP 2164.01(a), eight factors must be considered by an Examiner when determining whether a disclosure is enabling.

The Examiner, while properly citing the eight factors on page 5 of the Office Action, has failed to consider each of them fully when assessing enablement. Further, for those factors that are considered, the Examiner provides mainly conclusory statements. The rejection in the Office Action is based on two premises: first, that the specification only discloses *in vitro* examples for the effects of OP-1 on hippocampal dendrites, and second, that *in vitro* experiments cannot be extrapolated to the *in vivo* effects of OP-1 on memory formation. Both of these premises are unsubstantiated in the Office Action.

The first premise is false because it ignores Examples 1-14 of the originally-filed specification. These examples teach in great detail, *inter alia*, how morphogens may be used to increase memory in a mammal having hippocampal tissue damaged by neurotoxins (Example 7), transient global ischemia (Example 8), permanent global ischemia (Example 9), or traumatic brain injury (Example 10). Examples 11-13 teach, *inter alia*, methods of assaying declarative memory in mammals treated with a morphogen, and Example 14 describes, *inter alia*, an assay for measuring spatial memory.

Even though these examples in the specification are prophetic, they are sufficiently detailed to allow one skilled in the art to practice the invention without undue experimentation. In fact, the Office Action itself has acknowledged that a prophetic example describing an *in vivo* experiment is sufficient to enable. On page 9, the Office Action cites Example 18 in U.S. Patent No. 6,723,698 as anticipating the claimed invention, even though Example 18 is a prophetic example describing an *in vivo* experiment. Since a reference must be enabling to anticipate (MPEP 2121.01), the Examiner has conceded that prophetic examples are sufficient to enable the claims. (Applicants show in the next section that although enabling as a prophetic experiment for what it describes, example 18 in the '698 patent nevertheless fails to anticipate the pending claims for, *inter alia*, failing to teach all their elements.)

The second premise, that *in vitro* experiments cannot be extrapolated to *in vivo* effects on memory formation, is unsupported in the Office Action. Relying on the Charron reference, the Office Action alleges that Shh and BMP *gradients* are necessary for the formation of commissural axon, and that it is unclear how the morphogens of the invention would be administered to achieve the gradients.

The Charron reference, however, is not germane to the claimed invention. The Office Action fails to provide any evidence that Shh, let alone its gradients, is required for practicing the invention. The Office Action fails to establish that (1) gradients of Shh and BMP acting during embryogenesis have any role in treating a post-embryonic mammal; (2) that gradients of Shh and BMP acting during *development* have a function in the treatment of damaged tissue; or that (3) gradients regulating axonal formation are also needed for dendritic formation.

Not only has the Office Action failed to establish any evidence for these three assumptions, the examples in paragraphs 174-179 contradict them. These examples demonstrate that contacting a

culture of hippocampal neurons with OP-1 induces dendrite formation in the absence of any exogenous Shh and in the absence of any OP-1 gradients. And even if OP-1 gradients were required for dendrite growth, which the Office Action has failed to establish, the specification teaches, as one of the modes of administration, that the morphogen may be administered intraventricularly through canuli (see example 1); canuli might be expected to create a gradient in the brain as the morphogen diffuses out of the canuli.

In sum, the Office Action has failed to apply all eight of the *Wands* factors, and instead largely relies on the Charron reference whose teachings fail to undermine the enablement of the claims. In view of the arguments set forth above, Applicants respectfully request reconsideration and withdrawal of this ground of rejection.

**Claim rejection under 35 U.S.C. § 102(e)**

The Office Action maintains the rejection of claims 27-38, and further rejects claims 39-46 and 48-50, under 35 U.S.C. § 102(e), alleging that these claims are anticipated by U.S. Patent No. 6,723,698 ("the '698 Patent").

Without conceding the correctness of this ground of rejection, Applicants have canceled claims 39-42, 45, 47, 49 and 50.

Applicants have amended claim 27 to recite a method for reducing memory dysfunction associated with damaged hippocampal tissue in a mammal "and caused by permanent or transient global ischemia." The Examiner alleges that the '698 patent teaches ischemia. However, the '698 patent does not refer to hippocampal damage caused by permanent or transient global ischemia. A claim is anticipated "only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." MPEP § 2131.01. Because it does not teach or suggest each and every element as set forth in the claim, the '698 Patent does not anticipate independent claim 27 or dependent claims 28-32, 34-38, 43 or 44.

The Examiner further contends that the '698 patent teaches the use of biocompatible microspheres to deliver OP-1 as in claim 44 of the present invention. Applicants point out that the '698 patent does not refer to microspheres, or to spheres of any kind, and therefore fails to anticipate claim 44.

The Examiner further alleges that the '698 patent teaches administration of OP-1 to prevent neuronal cell death caused by trauma from chemicals including ethanol, as in claim 46 of the present invention. To expedite allowance of the claims, Applicants have amended claim 46 to delete the reference to ethanol and lead. The other neurotoxins recited in claim 46, ibotenic acid, ammonia and formaldehyde, are not referred to in the '698 patent and therefore are novel.

The Examiner argues that the '698 patent teaches administration of OP-1 to prevent neuronal cell death caused by malnutrition or metabolic disorders, as in claim 48 of the present invention. However, Applicants note that malnutrition and metabolic disorders are merely mentioned in the introduction of the '698 patent as potential causes of neuropathy. Nowhere in the '698 patent is there reference to the administration of OP-1 to improve cognitive function in patients afflicted with neuropathies caused by malnutrition or metabolic disorders.

Applicants respectfully request reconsideration and withdrawal of the rejection.

**Claim rejection under 35 U.S.C § 112**

The Office Action rejects claim 34 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. The Examiner alleges that the range of 293-431 of SEQ ID NO:2 is not disclosed in the specification. In response, Applicants submit that claim 34 has been amended, rendering this rejection moot.

Applicants respectfully request reconsideration and withdrawal of this ground of rejection.

**Claim rejection under 35 U.S.C § 103(a)**

The Office Action rejects claims 27-50 under 35 U.S.C. 103(a) as unpatentable over the '698 Patent in view of Kern et al. The Examiner contends that lead has been shown to cause neurotoxic effects on hippocampal neurons (as allegedly referred to by Kern et al.), and OP-1 has been shown to be neuroprotective for neuronal damage caused by chemical/physical/neurotoxic trauma (as allegedly referred to by the '698 patent). The Examiner argues that it would thus have been obvious for the skilled artisan at the time the invention was made to administer OP-1 to prevent neuronal damage due to the toxicity of lead.

Without conceding this ground of rejection, but merely to expedite allowance of the claims, Applicants have canceled claim 47, thereby obviating this rejection.

**CONCLUSION**

In view of the above arguments, Applicant believes the pending application is in condition for allowance.

Applicant believes no fee is due with this response in addition to those listed on the fee transmittal sheet. However, if an additional fee is due, please charge our Deposit Account No. 18-1945, under Order No. JJJ-P02-510 from which the undersigned is authorized to draw.

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Respectfully submitted,

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